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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Darby & Darby
805 Third Avenue
New York, NY 10022-7513

EXAMINER	
MCGAW, MICHAEL M	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,316	STEINMAN ET AL.	
	Examiner	Art Unit	
	Michael M. McGaw	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35 and 37-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

The objections to the specification are withdrawn in light of Applicant's amendments.

Claim Rejections - 35 USC § 103

Claims 35 and 37-39 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Wong, C. et al. in view of Khanna, R et al. (1999) and/or Khanna, R et al, (1997). This rejection is maintained for the reasons indicated below.

Response to Arguments

Applicant's arguments filed October 12, 2004 have been fully considered but they are not persuasive.

Applicant claims a "method for making an EBV protective dendritic cell, which method comprises contacting a human dendritic cell with EBNA-1 *ex vivo*."

As a preliminary matter, the aforementioned claim is directed to an "*EBV protective* dendritic cell." (emphasis added) The Examiner is unable to find a definition for "EBV protective" in the specification. On page 30 of the specification the term protect is defined "to mean for the treatment or prevention of Epstein Barr Virus infection." The Examiner is interpreting EBV protective as specifying that an immunogenic response is raised as a result of the administration of the cell made by the method claimed.

Applicant generally asserts on page 5 of the Response that "None of the references cited with Wong would have provided one of ordinary skill in the art with a reasonable expectation that an EBNA-I contacted human dendritic cell would be protective against EBV." More specifically, Applicant asserts "Khanna 1999 does not disclose or suggest a human dendritic cell pulsed with EBNA-I that is protective against EBV." Addressing Khanna 1999 Applicant concludes:

> Khanna 1999 suggests that CTLs would (1) not react to an EBNA-I contacted dendritic cell or, (2) if a CTL did react with such a dendritic cell, the resulting CTL would only recognize target cells to which recombinant EBNA-I has been supplied. Neither of these scenarios provides any expectation that a dendritic cell pulsed with EBNA-I would successfully protect against EBV infection. Furthermore, the absence of CTL responses to EBNA-I in most healthy virus carriers suggests that immunity to EBNA-I has no protective value.

First, Applicant asserts that, based upon the teachings of Khanna 1999, CTLs would not react to an EBNA-I contacted dendritic cell. In fact, Khanna 1999 teaches exactly the opposite. Khanna states on page 51 "EBNA1-specific CTLs can only recognize LCLs to which recombinant EBNA1 protein has been supplied exogenously thus indicating that the GAr-mediated inhibitory effect is not effective if EBNA1 is loaded through the exogenous pathway." Thus, Khanna teaches that EBNA1 can be processed via the exogenous pathway ultimately leading to presentation through MHC class II molecules to CD4+ T cells. In making this statement Khanna 1999 references Khanna 1997. In the abstract to Khanna 1997 it is stated "Using purified EBNA1 protiein, we demonstrate here that CD4+ CTL can efficiently recognize EBV-transformed B-cells...following exogenous sensitization with this antigen, and this immune recognition is not affected by the G-Ar domain within EBNA1."

Therefore, where a CTL has been demonstrated to react with another EBNA1 contacted cell, as Khanna 1997 demonstrates, one would have every reason to expect a CTL to also react with an EBNA1 contacted dendritic cell. Moreover, the CTLs responding to the EBNA1 presented by the dendritic cell would further the immune reaction. It is known that the development and persistence of CD8+ T cells are dependent on CD4+ T cell help. (See Khanna 1997 on page 1542 discussing the importance of CD4+ T cells in the priming and effector phases of the anti-tumor response; also note that Applicant admits as much on pages 2-3 of the specification.) Moreover, dendritic cells are known to be potent antigen presenting cells for CD4+ and CD8+ T cell immunity. Thus, EBNA1 presented via dendritic cells would be expected to expand the population of CD4+ and CD8+ EBNA1-specific CTLs in healthy carriers. In particular, cross-priming by the dendritic cells would also expand CD8+ populations. Khanna 1999 states "It is important to mention here that recent studies have suggested that the GAr-mediated protections from processing may on occasion be overridden *in vivo*, since both CD4+ and CD8+ EBNA1-specific CTLS have been detected in healthy virus carriers." Thus, these CD4+ and CD8+ EBNA1-specific CTL populations would be increased by the EBNA1 contacted dendritic cells. Khanna 1999 also indicates "preliminary studies carried out in our laboratory strongly suggest that specific targeting of EBNA1 through the proteasomal pathway can also restore endogenous processing through the class I pathway." For these reasons, Khanna 1999 does not suggest that immunity to EBNA1 has no protective value.

Next, Applicant asserts "Rickenson falls far short of providing a reasonable expectation of success for a human dendritic cell contacted with EBNA-I that is protective against EBV infection. On the contrary, this reference creates a great deal of doubt as to whether the invention would work."

It is first noted that Rickenson did not form part of the rejection, but instead was cited to support the proposition that it is widely known that LMP2 is one of only three predominant, latency-associated antigens. The other two are EBNA1 and LMP1. This was relevant to the Wong et al reference, which taught a dendritic cell contacted with LMP2 of EBV. Rickenson was cited to support the proposition that it is widely known to focus on these three antigens in the present context. Specifically, Rickenson states, "Therapeutic strategies must therefore seek to identify and exploit CTL responses which may be minor components of memory but which are directed against epitopes in EBNA1 (if such exist), LMP1, or LMP2, i.e., antigens that are expressed in the tumor cells." As to the existence of EBNA1 epitopes, Khanna, as discussed above, solves this dilemma. Whether one would have been discouraged as to the expectation of success based upon Rickenson's teachings is made moot by the subsequent teachings by Khanna towards Applicant's invention.

On page 6 Applicant states "Khanna 1997 suggests only 'a possibility' of immune targeting class I processing defective EBV-associated malignancies (Khanna 1997, page 1542, 2 column), though it is hard to see even a possibility if CTLs could not recognize EBNA-I." First, it has been pointed out above that CTLs do recognize EBNA1 as taught by Khanna. Moreover, assuming arguendo the existence of the 'possibility'

raised by Applicant, "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976)" See MPEP 2143.02. The requisite predictability was demonstrated by the combined teachings of Wong and Khanna. In response, Applicant has argued that Khanna 1997 suggests only 'a possibility' of success. Assuming this to be the case, this is certainly more than providing evidence of "no reasonable expectation of success" as required under MPEP 2144.02 to rebute a *prima facie* case of obviousness. Therefore, the arguments are not found persuasive.

Applicant indicates on page 6 of the Response that "such a dendritic cell would have no value since no protection is afforded against EBV infection by EBNA-I-specific CTLS that either do not 'see' or see but cannot destroy EBV-infected cells." The examiner disagrees with this proposition. First, such a dendritic cell would stimulate an antibody response to EBNA1, which would constitute an immune response against EBV. Second, the dendritic cell would produce chemokines, cytokines and IFN-α/β. Among other things, this would presumably enhance the CTL response against other EBV peptides such as LMP1 and LMP2, noted by Khanna to be inherently weak. (See page 60 of Khanna 1999) It is also possible that the CD4+ T cells may be directly involved in the lysis of EBNA1 expressing cells. CD4+ and CD8+ EBNA1-specific CTL populations would be increased by the EBNA1 contacted dendritic cells. Moreover, Khanna 1999 indicates on page 51 that mechanisms exist whereby endogenous

processing through the class I pathway can be restored, which would make an expanded CD4+ and CD8+ CTL population very desirable. For these reasons Applicant's arguments are not found persuasive.

Applicant indicates on page 6, "In sum, Khanna 1997 does not disclose or suggest a human dendritic cell contacted with EBNA-I that is protective against EBV..." In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The *combination* of Wong, C. et al (1998) in view of Khanna, R. et al. (1999) renders Applicant's invention obvious.

Conclusion

Claims 35 and 37-39 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael M. McGaw whose telephone number is (571) 272-2902. The examiner can normally be reached on Monday through Friday from 8 A.M. to 5 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

M.M.

Michael M. McGaw

Monday, December 27, 2004

JAMES HOUSEL 1/10/05
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600